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LETTERS TO THE EDITOR

Increased Iron Deposition Is Directly Associated With Myocardial Dysfunction in Patients With Sickle Cell Disease

Cardiac toxicity from myocardial iron deposition has been well established in beta-thalassemia major (1). Among patients with thalassemia who are transfusion dependent, cardiac toxicity from myocardial iron deposition remains a major cause of mortality. Myocardial iron deposition, although less common, can also occur in frequently transfused patients with sickle cell disease (SCD) (2).

Magnetic resonance imaging (MRI) is the reference standard to evaluate myocardial iron overload and efficacy of the iron chelation therapy over time. Myocardial deformation analysis using speckle-tracking echocardiography (STE) has been increasingly adopted to assess left ventricular function. The aim of this study was to determine if myocardial iron concentration (MIC), estimated from T2* MRI, correlates with myocardial dysfunction assessed by STE.

Fifteen SCD patients who had abdominal MRI scans and echocardiography performed within a 1-year period were retrospectively selected. The abdominal MRI studies were acquired using 1.5- or 3-T scanners (Philips Healthcare, Andover, MA). All studies included at least 1 dual echo gradient echo. T2* was derived from the following equation: $T2^* = (TE_{out} - TE_{in})/\ln(SI_{in}/SI_{out})$, where TE stands for time echo, ln for natural logarithm, SI for signal intensity, out for out-of-phase, and in for in-phase. MIC was estimated using the clinical calibration equation: $[Fe] = 45.0 \times (T2^*)^{-1.22}$, with [Fe] in mg/g dry weight (dw) (3).

The associations between MIC and STE were evaluated. Statistical analysis was performed using SPSS version 21 (IBM Corporation, Armonk, New York). Spearman correlation coefficients were calculated, and a p value <0.05 was considered statistically significant. The 95% confidence interval for the Spearman correlation coefficient was calculated using Fisher z-transformation.

SCD patients median age was 34 years (range 21 to 70 years), 9 (60%) were women. MIC was 0.929 ± 0.832 mg/g dw (range 0.0171 to 2.77 mg/g dw). As shown in **Table 1**, conventional echocardiography indices of left ventricular systolic and diastolic function did not correlate with MIC. In contrast, radial STE parameters showed a strong association. In fact, in our study group, radial displacement <5 mm was found in 5 of 6 subjects with a MIC >1 mg/g, whereas radial displacement ≥5 mm was found in all subjects with a MIC <1 mg/g. In an age-matched control group with normal MIC, 9 of 10 showed radial displacement ≥5 mm.

This preliminary study demonstrates a strong correlation between MIC and the presence of subclinical myocardial dysfunction, as determined by STE, in patients with SCD. These findings are noteworthy because the MIC values in our study subjects were only mildly elevated. Normal MIC has been previously reported as 0.34 mg/g dw (range 0.29 to 0.47 mg/g dw). In our SCD patient group, 8 subjects had a MIC >0.47 mg/g.

STE parameters have been previously evaluated in SCD. Barbosa et al. (4) showed that STE measures in SCD were similar to controls without SCD. In contrast, our study group had lower longitudinal and radial strains. This may be due to differences in the populations studied. The patients in the study by Barbosa et al. (4) were younger and were not evaluated for MIC, whereas our population included older patients with longer duration of disease.

Our study has some important limitations. First, it is a retrospective study with a small sample size. Second, T2* values were calculated from the myocardial signal obtained from abdominal MRI studies because they were more commonly indicated for the evaluation of symptoms. Accordingly, motion artifacts from MRI images acquired without electrocardiogram gating may have resulted in inaccuracies in determining MIC. Third, we used MRI images obtained by both 1.5- and 3-T scanners because of the limited number of study subjects with images from a single scanner. Although 3-T scanners are now commonly used, there is less clinical experience in measurement of MIC using 3-T.

These preliminary results showing a decrease in radial deformation detected by STE correlating with increased MIC in patients with SCD do not prove a causative relationship. However, given the known cardiac toxicity of myocardial iron, STE may identify iron overload at an early stage, potentially guiding chelating therapy. Larger prospective studies will be needed to investigate the association of MIC, STE,

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TABLE 1 Correlations Between MIC and Echocardiographic Variables

	ρ	95% CI	p Value
Conventional echocardiographic parameters			
EF	0.24	−0.32 to 0.66	0.40
E/A	0.52	−0.070 to 0.82	0.071
Deceleration time	−0.058	−0.59 to 0.51	0.85
e′	0.52	−0.039 to 0.82	0.059
E/e′	−0.43	−0.80 to 0.21	0.17
Echocardiographic speckle-tracking analysis			
Radial strain, %	−0.55	−0.82 to −0.026	0.036
Radial displacement, mm	−0.72	−0.90 to −0.31	0.0025
Radial velocity, cm/s	−0.82	−0.93 to −0.51	0.0002
Circumferential strain, %	0.75	0.36 to 0.91	0.0014
Circumferential strain rate, 1/s	0.44	−0.11 to 0.77	0.10
Longitudinal strain, %	0.30	−0.26 to 0.70	0.28
Longitudinal strain rate, 1/s	0.12	−0.42 to 0.59	0.67

EF = ejection fraction; MIC = myocardial iron concentration.

and adverse cardiac outcomes in patients with SCD as well as potential benefits from iron chelation.

Kana Fujikura, MD, PhD*
Anjani D. Golive, MD
Tomo Ando, MD
Francisco M. Corado, MD
Sanyog G. Shitole, MBBS, MPH
Jorge R. Kizer, MD, MSc
Aman M. Shah, MD
Martin R. Prince, MD, PhD
Daniel M. Spevack, MD, MPH
Mario J. Garcia, MD

*Cardiology Division, Department of Medicine
Montefiore Medical Center/Albert Einstein
College of Medicine
111 East 210th Street
Bronx, New York 10467
E-mail: kfujikura@bwh.harvard.edu

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Automated Quantification of Coronary Plaque Volume From CT Angiography Improves CV Risk Prediction at Long-Term Follow-Up

Accurate detection and quantification of localized but also diffuse coronary artery plaques from coronary computed tomography angiography and further differentiation of plaque tissue based on attenuation values may allow for outcome prediction of patients (1–3). The purpose of this analysis was to assess the predictive value of quantified coronary total plaque volume (TPV), low-attenuation plaque volume (LAPV), and positive remodeling (PR) using an automated software approach in a large cohort of consecutive patients with a 5-year follow-up.

The patient population, the coronary computed tomography angiography procedure, and the calculation of the Agatston score have been described in detail elsewhere (4). An automated and validated software was used to perform plaque volume quantification (QAngio CT Research Edition V2.1.16.1, Medis Medical Image Systems BV, Leiden, the Netherlands) in all 4 major coronary vessels with a luminal diameter >1.5 mm (1,2). All detected plaques were summed up for every patient to obtain TPV per patient. To obtain LAPV an algorithm that accounts for different enhancement patterns in lesions and distal parts of vessels was applied (2). PR was calculated by the software and refers to outer vessel wall diameter increase inside a plaque when compared with the proximal outer vessel wall reference diameter.

All-cause mortality and myocardial infarction (MI) served as primary endpoint. Cardiac death and acute coronary syndrome were defined as secondary cardiac endpoint. The Youden index derived from receiver operating characteristic curve analysis was used to determine optimal thresholds for risk stratification of patients into different risk groups.

Analysis is based on 1,577 patients with a median follow-up of 5.5 years (interquartile range: 5.0 to 6.2 years). The primary endpoint of all-cause mortality and MI occurred in 61 patients (48 patients died, 13 suffered from MI). The secondary cardiac endpoint occurred in 30 patients (12 patients died from cardiovascular causes and 18 experienced acute coronary syndrome). The automated plaque analysis identified 2.2 ± 3.3 plaques per patient, a mean TPV of 88 ± 181 mm^3, and a mean LAPV of 1.6 ± 4.2 mm^3. Patients suffering from the primary endpoint had significantly more plaques (3.9 ± 3.7 vs. 2.2 ± 3.3;